

Use of Biomarkers for FDA Regulatory Decision Making In Division of Metabolism and Endocrinology Products

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DEFINITION

■ NIH Working Group Definition

- A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

Clinical Application of Biomarkers

- not a novel concept
- relied upon in clinical practice to guide decisions regarding treatment
 - Screening for preclinical disease (e.g., BP monitoring)
 - Diagnostic tool in detecting disease (e.g., troponin levels, treadmill testing)
 - Risk stratification (e.g., tumor grading and staging)
 - Guide selection or titration of therapy (e.g., treatment goals for cholesterol)

Clinical Application of Biomarkers

- Relied upon for drug development
 - Biomarkers for screening, diagnosis, prognostication, and treatment decisions also applicable in drug development
 - As surrogate endpoints for drug approval where the biomarker can be viewed as.....
 - “a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy.”

Clinical Applications of Biomarkers

- Overlap b/w use in clinical practice and drug development
 - Assay sensitivity/specificity (true positives/true negatives)
 - predictive value of the test (probability of a correct diagnosis)
 - Independent predictor of disease or outcome vs. associated w/ disease or outcome
 - Change in biomarker parallels change in disease course
 - Clinical applicability (patient acceptance, cost, ease of interpretation)

Clinical Applications of Biomarkers

- More unique to drug development
 - Help identify toxicities early (animal studies, Phase 1 and 2) to direct resources to more promising candidate drugs
 - Selection of dose or population to pursue in pivotal trials
 - Financial gains vs financial risks
 - Regulatory hurdles
 - Surrogate endpoint – the Holy Grail of Drug Development

CV Biomarkers Specific to DMEP

- Experience established w/ several biomarkers relied upon as surrogate endpoints and basis of approval for several marketed drugs
 - Cholesterol reduction (LDL-C, Total-C)
 - Glycemic control (HbA1c)

Established Biomarkers

- Evidence favoring use of such biomarkers includes
 - Extensive and consistent epidemiologic support (different cohorts/patient population) demonstrating correlation b/w biomarker and risk of disease
 - Animal models and/or genetic disorders
 - RCTs in which targeting the biomarker impacts disease outcome
 - Effect of biomarker on clinical outcome consistent in drug class or across drug classes
 - Favorable effect of targeting biomarker on various clinical presentation of disease (CV death, nonfatal MI, stroke, microvascular complications of DM)
- Mountains of evidence for benefit of biomarker + extensive clinical exposure of drug = favorable candidate for drug approval

What next in DMEP?

- Reasonable to expect that the weight of evidence applied to currently accepted biomarkers will be similarly applied for new biomarkers
- Few emerging biomarkers have good evidence favoring a critical role in drug development
- Most are not ready for prime time or a place in labeling but may play a supporting role in drug development

Potential Uses of New Biomarkers in DMEP

- Selecting out target population
 - Risk stratification or selecting out drug responders
- Dose selection
 - Phase 2 dose-finding studies; rely on biomarker to narrow the candidates to a few to take into Phase 3
- Exploring pharmacologic effect of drug
 - Exploratory – correlate change in new biomarker w/ the accepted surrogate
- Comparative efficacy or safety
 - Address the difficulties and expense of head-to-head studies

.....in selecting a study population

- Already doing this with established biomarkers but new biomarkers can be applied to:
 -select a higher risk population
 - Example – baseline CRP levels
 -or a population that is more likely to respond to drug
 - Example – impaired glucose tolerance, C-peptide levels
 -or a population that better establishes the safety profile of the drug
 - Example – NYHA Class II CHF patients, baseline BNP levels for PPAR agonists

....in dose selection

- Select doses for pivotal study based on biomarker establishing minimally effective and maximally tolerated dose
- characterize a range of effective doses using a biomarker that can be assessed in a shorter period of time
 - Example: HbA1c requires ~12 wks but FPG, PP glucose or fructosamine may predict a dose range sooner
- Select doses based on biomarker that might confer an advantage over other marketed products
 - Example: TG-lowering or HDL-raising with a PPAR agonist being developed for treatment of diabetes; comparative rates of peripheral edema or weight gain
- Pros: may shorten development time – condensed Phase 2/3 program – seamless adaptive trial designs
- Cons: biomarker not truly predictive of response based on acceptable surrogate endpoint

....in exploring new mechanisms of
action

- Assessing efficacy of drug on some other pathogenic process contributing to the disease
 - Example 1: inflammatory markers in atherosclerosis
 - Example 2: glucose-dependent release of insulin

....in active controlled trials

- Given the time and expense, head-to-head comparisons of drugs' effects on clinical outcome rarely undertaken ----- also risk to product that is shown to be less efficacious
- Active control studies to compare efficacy or safety b/w drugs may look to biomarkers (e.g., imaging modalities)

Conclusions

- Some things don't change even with *change* in leadership
 - D. Orloff, 2005 CV Biomarkers Symposium
 - “Effects on biomarkers provide only preliminary proof of benefit (a picture is, in the end, only a picture).”
 - “Endpoint studies are, in the end, the only confirmation of clinical benefit.”
- Biomarker → Surrogate Endpoint
 - Mountains of evidence for benefit of biomarker + extensive clinical exposure of drug = favorable candidate for drug approval
 - The surrogate endpoint is still just a substitute for some clinically meaningful endpoint
 - Even established biomarkers have cautionary tales (Baycol, Rezulin, and other PPARs)

Conclusions (cont'd)

-however, some drug failures reflected rare side-effects not typically observed in pre-marketing database... not necessarily negating the evidence for the relying on the biomarker
-continue to apply scientific principles for developing and evaluating biomarker
- While few will become the validated surrogate for clinical benefit, most will help in establishing safe and effective therapies during clinical development